

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Publication number:

0 434 385 A2

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 90313899.8

(51) Int. Cl.⁵: **A61K 31/395**

(22) Date of filing: 19.12.90

The title of the invention has been amended
(Guidelines for Examination in the EPO, A-III,
7.3).

(30) Priority: 21.12.89 US 454418

(43) Date of publication of application:
26.06.91 Bulletin 91/26(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

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(54) Use of macrocyclic nitrogen containing compounds for the treatment of retroviral infections.

(57) Pharmaceutical compositions containing as active ingredients a linked cyclic compound of the general formula I

Z - (A)_n - Y (I)

in which Z and Y are independently polyheterocyclic moieties having from 9 to 32 ring members and from 3 to 8 amine heteroatoms, especially nitrogen, in the ring, A is a linking atom or group, and n is 0 or an integer from 1 to 6, are indicated for the treatment of viral infections, and preventative administration, especially for retroviral infections.

IMPROVEMENTS IN CHEMICAL COMPOUNDS

This invention concerns improvements in chemical compounds, more especially it concerns compounds and pharmaceutical compositions. In particular it concerns compositions and compounds having activity in *in vitro* tests on Human Immunodeficiency Virus-infected cells.

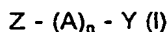
The disease known as Acquired Immune Deficiency Syndrome (AIDS) caused by infection by HIV has attracted immense research effort because of the effects of the disease on infected individuals and the dangers of the disease spreading to a wider section of the population. In general, although various chemotherapeutic treatments have been advocated, and some compounds have emerged as a potential basis for treatment, there is still a need for alternatives. In particular, most treatments such as the compound known as AZT have a high toxicity to cells, and it would be desirable to find compounds which are less toxic. In man, the development of resistance to AZT has been identified as an additional clinical problem.

We have found a group of compounds which show protective properties in *in vitro* screens of cells challenged with HIV-1 and/or HIV-2, and are therefore indicated as having potential for the treatment of AIDS and AIDS Related Complex and other viral and especially retroviral infections. Accordingly, the present invention provides the use of compounds defined below, in pharmaceutical compositions for treating HIV-infected patients. The invention further provides pharmaceutical compositions comprising a said compound in combination or association with a pharmaceutically acceptable diluent or excipient, for the treatment of HIV-infected patients. The invention may also be defined as the use of a said compound for the manufacture of a medicament for the treatment of HIV-infected patients. The invention further provides a process for the production of a pharmaceutical composition for the treatment of a HIV-infected patient, comprising the combination of a compound as defined below with a pharmaceutically acceptable diluent or excipient, and formulating said composition into a form suitable for administration to said patient. The invention also provides a method of treatment of an HIV-infected patient, comprising administering to said patient an effective dose of a said compound. It is to be understood that treatment includes prophylactic treatment of patients at risk, in view of the protective properties observed. Whilst this description is especially directed to combating HIV, this invention includes other aspects in which other diseases may be treated, including for example microbial infections.

A 2,2'-dimer of cyclam has been reported as being isolated as a 2% by-product in the synthesis of cyclam (1,4,8,11-tetraazacyclotetradecane) (Barefield et al, J.C.S. Chem. Comm. (1981), 302). This compound was stated to be insoluble in water. We believe that the insoluble 2,2'-bicyclam is a mixture of the 2R,2'R and 2S,2'S enantiomers; we have characterised a soluble dimer which we believe to be the meso 2R,2'S isomer. The 6,6'-bicyclam isomer has been reported by Fabbri et al, Inorg. Chem. 25, 2671 (1986). Certain N,N'-linked bicyclic compounds have been reported by Ciampolini et al, Inorg. Chem. 26, 3527 (1987). No biological activity has been suggested for such compounds.

US Patent 4,156,683 discloses monocyclic and bicyclic macrocyclic compounds, which are said to have biological activity in regulating sodium, potassium and calcium levels in mammals. Additionally, a specific group of N-alkylated monocyclic compounds are said to possess activity against A₂ influenza viruses in a modified Hermann test on chick fibroblast tissue. It is also said that the preferred compounds, which form complexes of greater stability, are those having three bridging chains between bridgehead nitrogen atoms, that is fused bicyclic compounds.

The present invention provides as active compounds linked cyclic compounds of the general formula I



in which Z and Y are independently polyheterocyclic moieties having from 9 to 32 ring members and from 3 to 8 nuclear heteroatoms in the ring, wherein the heteroatoms are selected from nitrogen, oxygen and sulphur,

A is a linking atom or group, and

n is 0 or an integer from 1 to 6. The invention also encompasses acid addition salts and metal complexes of the compounds of formula I.

In the above formula, A may be alkylene, for example 1,3 propandiyl, unsaturated alkylene or a group selected from aryl, fused aryl, polyoxo thylene, carboxylate, esters and amides, or a nitrogen or sulphur atom.

Each of the moieties Z and Y may contain nitrogen and/or oxygen and/or sulphur heteroatoms; preferably the moieties contain nitrogen atoms with optional further heteroatoms selected from oxygen and sulphur. A particular embodiment of the invention relates to compounds in which all the nuclear heteroat-

oms are nitrogen atoms.

The cyclic moieties may be substituted or unsubstituted, and may contain unsaturation. Suitable substituents may be selected from halogens, especially chlorine or bromine, $-\text{NH}_2$, $-\text{OH}$, $-\text{COOH}$, ester groups, $-\text{CONH}_2$ and alkyl or aryl groups, e.g. of up to 10 carbon atoms, which themselves may be substituted by the aforementioned substituents. Preferred moieties are those of 10 to 24 ring members, especially 12 to 18 ring members, and preferred numbers of nuclear nitrogen atoms are 4 to 6. It is convenient that the moieties are identical. The moieties may be linked by attachment to the carbon atoms or nitrogen atoms of the ring, ie C-C, N-N, C-N.

The invention also includes what may be termed "pro-drugs", that is protected forms of the linked macrocyclic compounds, which release the compound after administration to a patient. For example, the compound may carry a protective group which is split off by hydrolysis in body fluids, e.g. in the bloodstream, thus releasing active compound. A discussion of pro-drugs may be found in "Smith and Williams' Introduction to the Principles of Drug Design", H.J.Smith, Wright, 2nd Edition, London 1988.

A number of the active compounds according to the invention are known, and the compounds may be prepared by identical methods or methods analogous thereto.

The compounds are indicated for the treatment of viral infections, especially retrovirus infections and particularly HIV infections, and the compounds of formula I, are to be considered as active compounds for the pharmaceutical compositions, processes for making the same and methods of treatment mentioned above. In these aspects of the invention, it is to be understood that meso forms, enantiomers and resolved optically active forms of the compounds of formula I, are included. Also, it is to be considered within the invention, compounds of formula I diluted with non-toxic or other active substances. Acid addition salts, for example hydrochlorides, and non-toxic labile metal complexes of the compounds of formula I are also active compounds according to the present invention. Non-toxic in the present context has to be considered with reference to the prognosis for the infected patient without treatment. Zinc and nickel complexes are especially indicated, whereas less labile metal atoms such as cobalt and rhodium are less preferred because of likely lower selectivity.

The invention will now be described by way of example only. Characterised samples of compounds A-I were tested in the standard *in vitro* tests, described below.

The compounds of the invention were tested in a screen by the MTT method (J.Virol. Methods 120: 309-321 [1988]). MT-4 cells (2.5×10^4 / well) were challenged with HIV-1(HTLV-III_B) or HIV-2 (LAV-2 ROD) at a concentration of 100 CCID₅₀ and incubated in the presence of various concentrations of the test compounds, which were added immediately after challenge with the virus. After 5 days culture at 37 °C in a CO₂ incubator, the number of viable cells was assessed by the MTT (tetrazolium) method. Antiviral activity and cytotoxicity of the compounds are expressed in the table below as ED₅₀ (ug/ml) and CD₅₀ (ug/ml), respectively. The potential therapeutic usefulness was assessed by calculating a Selectivity Index (SI) corresponding to the ratio of CD₅₀ to ED₅₀. A control test was performed using the known anti-HIV treatment AZT, and a number of comparison compounds were also run through the screen as detailed below.

In the table below, the compounds screened were

- A cyclam, recrystallised (comparison only)
- B meso (2R,2'S ; 2S,2'R) bicyclam plus inactive diluent
- C 2R,2'R ; 2S,2'S bicyclam racemate. 8HCl
- 45 D 6,6'-bicyclam. 8HCl. 2H₂O
- E 1,1'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane.8HCl
- F 1,1'-(1,3-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane.8HCl
- H 1,1'-(1,6-hexanediyl)bis-1,4,8,11-tetraazacyclotetradecane.8HCl
- I 2,5,9,12,16,19,23,26-octaazaspiro-[14,14]-heptaicosane

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TABLE

Compound	Virus	CD ₅₀	ED ₅₀	SI
A	HIV-1	226	>500	<1
	HIV-2	266	54	5
B	HIV-1	298	0.21	1435
	HIV-2	299	0.32	928
C	HIV-1	172	0.12	1430
	HIV-2	200	0.62	322
D	HIV-1	58	0.33	178
	HIV-2	54	>200	<1
E	HIV-1	305.2	8.52	36
	HIV-2	316.9	94	

TABLE

	Compound	Virus	CD ₅₀	ED ₅₀	SI
5	F	HIV-1	>500	0.35	>1429
10		HIV-2	>500	0.87	>575
	H	HIV-1	238	0.54	441
15		HIV-2	232	0.55	422
20	I	HIV-1	217	0.91	239
		HIV-2	318	>500	<1
25	AZT (Comparison)	HIV-1	>1	<0.008	>125

30 In this field of study, it is considered that any compound exhibiting a Selectivity Index of greater than 5 has the potential for further study. HIV is one of the most challenging viruses to combat, and the results given above provide an indication of activity against other retroviruses and against other viruses in general.

Other compounds considered significant are:

methylene (or polymethylene) di-1-N-1,4,8,11-tetraaza cyclotetradecane
 3,3'-bis-1,5,9,13-tetraazacyclohexadecane
 35 3,3'-bis-1,5,8,11,14-pentaazacyclohexadecane
 5,5'-bis-1,4,8,11-tetraazacyclotetradecane
 2,5'-bis-1,4,8,11-tetraazacyclotetradecane
 2,6'-bis-1,4,8,11-tetraazacyclotetradecane
 1,1'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 40 1,1'-(1,3-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 1,1'-(1,4-butanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 1,1'-(1,5-pentanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 1,1'-(1,6-hexanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 3,3'-(bis-1,5,9,13-tetraazacyclohexadecane)
 45 3,3'-(bis-1,5,8,11,14-pentaazacyclohexadecane)
 3,3'-(bis-1,5,9,13-tetraazacyclohexadecane)
 3,3'-(bis-1,5,9,13-tetraazacyclohexadecane)
 1,1'-(1,2-ethanediyl)bis-1,5,9,13-cyclotetraazahexadecane
 1,1'-(1,3-propanediyl)bis-1,5,9,13-cyclotetraazahexadecane
 50 1,1'-(1,4-butanediyl)bis-1,5,9,13-cyclotetraazahexadecane
 1,1'-(1,5-pentanediyl)bis-1,5,9,13-cyclotetraazahexadecane
 1,1'-(1,6-hexanediyl)bis-1,5,9,13-cyclotetraazahexadecane
 rac-1,2'-bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,2'-(methanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 55 rac-1,2'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,2'-(1,3-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,2'-(1,4-butanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,2'-(1,5-pentanediyl)bis-1,4,8,11-tetraazacyclotetradecane

rac-1,2'-(1,6-hexanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,5'-(methanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,5'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,5'-(1,3-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 5 rac-1,5'-(1,4-butanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,5'-(1,5-pentanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,5'-(1,6-hexanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,6'-bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,6'-(methanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 10 rac-1,6'-(1,2-ethanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,6'-(1,3-propanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,6'-(1,4-butanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,6'-(1,5-pentanediyl)bis-1,4,8,11-tetraazacyclotetradecane
 rac-1,6'-(1,6-hexanediyl)bis-1,4,8,11-tetraazacyclotetradecane

15 The active compounds may be administered in the form of pharmaceutical compositions formulated according to well known principles and incorporating the compound, preferably in unit dose form, in combination with a pharmaceutically acceptable diluent or excipient. Such compositions may be in the form of solutions or suspensions for injection, or irrigation or be in capsule, tablet, dragee, or other solid composition or as a solution or suspension for oral administration or formulated into pessaries or
 20 suppositories or sustained release forms of any of the above or for implantation. Suitable diluents, carriers, excipients and other components are known. It may be desirable also to formulate a composition for topical administration such as an ointment or cream. The compounds of the invention may be used, in the form of a composition or alone, and possibly carried on a finely divided support, as a coating on devices which in use contact body fluids, to discourage transmission of viral infections. Examples of devices to be
 25 considered in this aspect of the invention are surgical devices and gloves and contraceptives such as condoms, and other items, appliances, wound dressings and coverings, implements etc. generally to be considered as devices according to this aspect of the invention.

The pharmaceutical compositions according to the invention may contain unit dosages determined in accordance with conventional pharmacological methods, suitably to provide active compounds in the
 30 dosage range in humans of from 0.1 to 100 mg/kg body weight per day, in a single dose or in a number of smaller doses. Preferred dosage ranges are 1 to 30 mg/kg body weight per day. Other active compounds may be used in the compositions or such other active compounds or supplemental therapy may be included in a course of treatment.

35 Claims

1. A pharmaceutical composition comprising an active ingredient selected from linked cyclic compounds of the general formula I

40 $Z - (A)_n - Y \text{ (I)}$

in which Z and Y are independently polyheterocyclic moieties having from 9 to 32 ring members and from 3 to 8 nuclear heteroatoms in the ring, wherein the heteroatoms are selected from nitrogen, oxygen and sulphur,

45 A is a linking atom or group, and
n is 0 or an integer from 1 to 6,

and their acid addition salts and metal complexes, in association or combination with a pharmaceutically acceptable diluent, carrier or excipient.

- 50 2. A composition according to claim 1, wherein each nuclear heteroatom is a nitrogen atom.
3. A composition according to claim 1 or 2, wherein each Z and Y moiety has 10 to 24 ring members.
4. A composition according to claim 3, wherein each Z and Y moiety has 12 to 18 ring members.
- 55 5. A composition according to any one of claims 1 to 4, wherein each Z and Y moiety has 4 to 6 amine nitrogen atoms in the ring.

6. A composition according to any one of the preceding claims, wherein n is 0.
7. A composition according to claim 1, wherein the active ingredient is 2,2'-bicyclam.
- 5 8. A composition according to claim 1, wherein the active ingredient is 6,6'-bicyclam.
9. A composition according to claim 1, wherein the active ingredient is 1,1-(1,3-propanediyl)bis-1,4,8,11-tetraaza cyclotetradecane.
- 10 10. A composition according to any one of the preceding claims, in unit dosage form for oral or parenteral administration.
11. A device or article which in use contacts body fluids, having a coating which comprises an active ingredient as defined in any one of claims 1 to 9.
- 15 12. The use of an active ingredient as defined in any one of claims 1 to 9, for the preparation of a medicament for the treatment of patients having, or at risk from, a viral infection.

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11 Publication number: **0 434 385 A3**

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21 Application number: **90313899.8**

51 Int. Cl.⁵: **A61K 31/395**

22 Date of filing: **19.12.90**

30 Priority: **21.12.89 US 454418**

43 Date of publication of application:
26.06.91 Bulletin 91/26

84 Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

88 Date of deferred publication of the search report:
04.03.92 Bulletin 92/10

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57 Pharmaceutical compositions containing as active ingredients a linked cyclic compound of the general formula I

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European
Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 31 3899

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 287 465 (GUERBET S.A.) * Page 9, lines 17-37; claims *	1-5	A 61 K 31/395
X	WO-A-8 808 422 (SCHERING AG) * Page 4, line 9 - page 6, line 19; claims *	1-5	
D,A	US-A-4 156 683 (LEHN) * Abstract; column 19, lines 15-35; claims *	1-12	
D,A	INORGANIC CHEMISTRY, vol. 26, no. 21, 1987, pages 3527-3533, American Chemical Society; M. CIAMPOLINI et al.: "Dinickel and dicopper complexes with N,N-linked bis(cyclam) ligands. An ideal system for the investigation of electrostatic effects on the redox behavior of pairs of metal ions" * Whole document *	1-12	
D,A	STN-INFORMATION SERVICE, FILE: CAS, AN: CHEMICAL ABSTRACTS, vol. 105, no. 8, abstract no. 71501m, Columbus, Ohio, US; L. FABBRIZZI et al.: "Ditopic receptors for transition-metal ions: a heterobimetallic nickel(II)-copper(II) bis(macrocyclic) complex and its stepwise oxidation to the tervalent state", & INORG. CHEM., 25(16), 2671-2	1-12	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
D,A	STN-INFORMATION SERVICE, FILE: CAS, AN: CHEMICAL ABSTRACTS, vol. 95, no. 5, abstract no. 43072d, Columbus, Ohio, US; E.K. BAREFIELD et al.: "Characterization of 2,2'-bis(1,4,8,11-tetraazacyclotetradecane): x-ray structure and properties of the dinuclear complex [Ni ₂ (C ₂₀ H ₄₆ N ₈)] [C ₁₀ O ₄] ₄ ", & J. CHEM. SOC., CHEM. COMMUN., (6), 302-4	1-12	A 61 K C 07 D
The present search report has been drawn up for all claims			
Place of search		Date of completion of search	Examiner
The Hague		16 December 91	GOETZ G.
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention</p> <p>E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons &: member of the same patent family, corresponding document</p>			